PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
VOSSIUS & PARTNER
Siebertstrasse 4
D-81675 München
GERMANY

EINGEGANGEN
Vossius & Partner
31. Jan. 2005
Frist 28.03.05
bearb.: 14.03.05 afr

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

29.05.05 22 Ro

(PCT Rule 44.1) Dokumente im Umschlag!

Applicant's or agent's file reference H1658 PCT S3	Date of mailing *(day/month/year)* 28/01/2005
International application No. PCT/EP2004/008547	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
Applicant UNIVERSITÄTSKLINIKUM MÜNSTER	International filing date *(day/month/year)* 29/07/2004

1. [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 740.14.35

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Angela Lopez Navarro

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international pbulication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
H1658 PCT S3		
International application No.	international filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP2004/008547	29/07/2004	29/07/2003
Applicant		
UNIVERSITÄTSKLINIKUM MÜNSTER		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 9 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      [ ] The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [X] **Certain claims were found unsearchable** (See Box II).

3. [ ] **Unity of invention is lacking** (see Box III).

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [ ] the text is approved as submitted by the applicant.
   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant.
      [ ] as selected by this Authority, because the applicant failed to suggest a figure.
      [ ] as selected by this Authority, because this figure better characterizes the invention.
   b. [X] none of the figures is to be published with the abstract.

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

The present invention relates to the use of at least one inhibitor of at least one ABC- transporter capable of transporting hyaluronan acorss a lipid bilayer, such as verapamil or valspadar, for the preparation of a pharmaceutical composition for the treatment of a disease which is associated with an excess transport of hyaluronan across a lipid bilayer, e.g. arthritis. Furthermore, the present invention relates to a method for screening a compound which is suitable for the treatment of a disease which is associated with an excess transport of hyaluronan across a lipid bilayer, e.g. arthritis. The present invention also relates to a method for screening a compound which reduces the transport of hyaluronan by (an) ABC-transporter(s). Furthermore, the present invention relates to a method for identifying a subject at risk for a disease which is associated with an excess transport of hyaluronan across a lipid bilayer, e.g. arthritis as well as to a method of screening for a compound which

is suitable for the treatment of a disease which is associated with an excess

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/277 A61K38/13 A61K31/4422 A61K31/64 A61K31/185
A61K31/343 A61K31/47 A61P19/02 G01N33/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, MEDLINE, WPI Data, PAJ, CHEM ABS Data, PASCAL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SALMON SYDNEY E ET AL: "Relevance of multidrug resistance to rheumatoid arthritis: Development of a new therapeutic hypothesis" JOURNAL OF RHEUMATOLOGY, vol. 23, no. SUPPL. 44, 1996, pages 97-101, XP009024606 ISSN: 0315-162X * abstract * * page 100, left column * ----- -/--	1-12, 37-46

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 January 2005	28/01/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Rodriguez-Palmero, M

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Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JORGENSEN C ET AL: "Multidrug resistances genes in rheumatology. Is their role immunological or pharmacological?" JOINT, BONE, SPINE: REVUE DU RHUMATISME. FRANCE JAN 2000, vol. 67, no. 1, January 2000 (2000-01), pages 8-10, XP009024585 ISSN: 1297-319X * page 8, right column, second and third paragraphs * * page 9, right column, 3rd paragraph *	1-12, 37-46
X	WO 92/16226 A (SMITHKLINE BEECHAM CORP) 1 October 1992 (1992-10-01) * page 4, 2nd last paragraph - page 5, 5th paragraph * * page 6, 3rd paragraph *	1-12, 37-46
X	WO 95/20385 A (MILES INC) 3 August 1995 (1995-08-03) * page 4, line 7 - page 8, line 5 * * page 12, table 1 * * page 13, table 2 * * claims *	1-12, 37-46
X	APPELBOOM THIERRY ET AL: "Proglumetacin versus indomethacin in rheumatoid arthritis: A double-blind multicenter study" ADVANCES IN THERAPY, vol. 11, no. 5, 1994, pages 228-234, XP009024731 ISSN: 0741-238X * abstract *	1-12, 37-46
X	KAGAN G ET AL: "FLUFENAMIC-ACID AND PLACEBO COMPARED IN RHEUMATOID ARTHRITIS AND OSTEO ARTHRITIS" JOURNAL OF INTERNATIONAL MEDICAL RESEARCH, vol. 9, no. 4, 1981, pages 253-256, XP009024706 ISSN: 0300-0605 * abstract *	1-12, 37-46
X	BROELL H ET AL: "Long time therapy with Benzbromaron in patients with arthritis urica" WIENER MEDIZINISCHE WOCHENSCHRIFT 1975, vol. 125, no. 38, 1975, pages 546-548, XP009024541 * page 548, left column, discussion *	1-12, 37-46

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HARRIS MARK ET AL: "Effect of low dose daily aspirin on serum urate levels and urinary excretion in patients receiving probenecid for gouty arthritis" JOURNAL OF RHEUMATOLOGY, vol. 27, no. 12, December 2000 (2000-12), pages 2873-2876, XP009024730 ISSN: 0315-162X * abstract *	1-12, 37-46
X	EP 1 136 552 A (BAYER AG) 26 September 2001 (2001-09-26) * page 15, paragraphs '0030! and '0031! *	1-12, 37-46
X	HARRIS RICHARD R ET AL: "Clinical activity of leukotriene inhibitors" INTERNATIONAL JOURNAL OF IMMUNOPHARMACOLOGY, vol. 17, no. 2, 1995, pages 147-156, XP002268320 ISSN: 0192-0561 * abstract * * page 154, left column, last paragraph - right column, 1st paragraph *	1-12, 37-46
X	LALIBERTE RON ET AL: "Tenidap modulates cytoplasmic pH and inhibits anion transport in vitro: II. Inhibition of IL-1-beta production from ATP-treated monocytes and macrophages" JOURNAL OF IMMUNOLOGY, vol. 153, no. 5, 1994, pages 2168-2179, XP002268321 ISSN: 0022-1767 * abstract * * page 2173, table II * * page 2177, right column, 3rd paragraph - page 2178, left column, 1st paragraph *	1-12, 37-46
X	ROBERT J: "Multidrug resistance in oncology: Diagnostic and therapeutic approaches" EUROPEAN JOURNAL OF CLINICAL INVESTIGATION, vol. 29, no. 6, June 1999 (1999-06), pages 536-545, XP002312388 ISSN: 0014-2972 cited in the application * page 541, column 2, paragraph 2 - page 542, column 2, second last paragraph *	1-7,11, 12,37, 41,42

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	√ANDERSSON RONNY ET AL: "Effects of interferon-alpha, verapamil and dacarbazine in the treatment of advanced malignant melanoma." MELANOMA RESEARCH, vol. 13, no. 1, February 2003 (2003-02), pages 87-91, XP009042117 ISSN: 0960-8931 * abstract *	1-7,11, 12,37, 41,42
X	YANG JIA-LIN ET AL: "Effect of nifedipine in metastatic colon cancer with DNA mismatch repair gene defect" LANCET (NORTH AMERICAN EDITION), vol. 357, no. 9270, 2 June 2001 (2001-06-02), pages 1767-1768, XP004244913 ISSN: 0099-5355 * abstract *	1-7,11, 12,37, 41,42
X	√MIDTVEDT K ET AL: "Nifedipine slow release reduces the incidence of acute rejections in hypertensive renal transplant recipients" NEPHROLOGY DIALYSIS TRANSPLANTATION, vol. 14, no. 9, September 1999 (1999-09), page A308, XP009042118 & ANNUAL CONGRESS OF THE EUROPEAN RENAL ASSOCIATION AND THE EUROPEAN DIALYSIS AND TRANSPLANT ASSOCIATI; MADRID, SPAIN; SEPTEMBER 5-8, 1999 ISSN: 0931-0509 * abstract *	1-7,11, 12,37, 41,42
X	√LAKE-BAKAAR G ET AL: "Dose-dependent effect of continuous subcutaneous verapamil infusion on experimental acute pancreatitis in mice" DIGESTIVE DISEASES AND SCIENCES, vol. 40, no. 11, 1995, pages 2349-2355, XP009042120 ISSN: 0163-2116 * abstract *	1-7,11, 12,37, 41,42
X	√DONG RAYMOND ET AL: "Verapamil ameliorates the clinical and pathological course of murine myocarditis" JOURNAL OF CLINICAL INVESTIGATION, vol. 90, no. 5, 1992, pages 2022-2030, XP002312390 ISSN: 0021-9738 * abstract *	1-7,11, 12,37, 41,42

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	APP E M ET AL: "ACUTE AND LONG-TERM AMILORIDE INHALATION IN CYSTIC FIBROSIS LUNG DISEASE A RATIONAL APPROACH TO CYSTIC FIBROSIS THERAPY" AMERICAN REVIEW OF RESPIRATORY DISEASE, vol. 141, no. 3, 1990, pages 605-612, XP009042112 ISSN: 0003-0805 * abstract *	1-7,11, 12,37, 41,42
X	WOO T Y ET AL: "Nifedipine in scleroderma ulcerations." INTERNATIONAL JOURNAL OF DERMATOLOGY. DEC 1984, vol. 23, no. 10, December 1984 (1984-12), pages 678-680, XP009042115 ISSN: 0011-9059 * abstract *	1-7,11, 12,37, 41,42
X	ABE K: "Effect of nicardipine hydrochloride on ischemic brain edema" NEUROLOGIA MEDICO-CHIRURGICA 1987 JAPAN, vol. 27, no. 9, 1987, pages 819-824, XP009042110 ISSN: 0387-2572 * abstract *	1-7,11, 12,37, 41,42
X	BENEDETTI A ET AL: "Treatment with amiloride, a Na+/H+ exchanger inhibitor, reduces hepatic stellate cells activation and collagen deposition in experimental liver fibrosis" HEPATOLOGY, vol. 26, no. 4 PART 2, 1997, page 334A, XP009042119 & 48TH ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES; CHICAGO, ILLINOIS, USA; NOVEMBER 7-11, 1997 ISSN: 0270-9139 * abstract *	1-7,11, 12,37, 41,42

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/008547

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 37-41 are directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9216226 A	01-10-1992	WO 9216226 A1	01-10-1992
WO 9520385 A	03-08-1995	US 5478848 A	26-12-1995
		AU 1606695 A	15-08-1995
		CA 2182114 A1	03-08-1995
		EP 0741568 A1	13-11-1996
		JP 9509655 T	30-09-1997
		NZ 279437 A	24-03-1997
		WO 9520385 A1	03-08-1995
EP 1136552 A	26-09-2001	EP 1136552 A1	26-09-2001
		AU 4419601 A	03-10-2001
		WO 0170810 A2	27-09-2001

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/008547	29.07.2004	29.07.2003

International Patent Classification (IPC) or both national classification and IPC
A61K31/277, A61K38/13, A61K31/4422, A61K31/64, A61K31/185, A61K31/343, A61K31/47, A61P19/02,

Applicant
UNIVERSITÄTSKLINIKUM MÜNSTER

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Rodriguez-Palmero, M

Telephone No. +49 89 2399-7871

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☐ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 37-41 with respect to industrial applicability

because:

☒ the said international application, or the said claims Nos. 37-41 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	13-36, 42-46
	No:	Claims	1-12, 37-41
Inventive step (IS)	Yes:	Claims	13-36
	No:	Claims	1-12, 37-46
Industrial applicability (IA)	Yes:	Claims	1-36, 42-46
	No:	Claims	-

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 37-41 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The following documents are referred to in this communication:

D1: SALMON SYDNEY E ET AL: "Relevance of multidrug resistance to rheumatoid arthritis: Development of a new therapeutic hypothesis" JOURNAL OF RHEUMATOLOGY, 1996, 23(SUPPL. 44):97-101.

D2: JORGENSEN C ET AL: "Multidrug resistances genes in rheumatology. Is their role immunological or pharmacological?" JOINT, BONE, SPINE: REVUE DU RHUMATISME, JAN 2000, 67(1):8-10.

D3: WO 92/16226 A (SMITHKLINE BEECHAM CORP) 1 October 1992.

D4: WO 95/20385 A (MILES INC) 3 August 1995.

D5: APPELBOOM THIERRY ET AL: "Proglumetacin versus indomethacin in rheumatoid arthritis: A double-blind multicenter study" ADVANCES IN THERAPY, 1994, 11(5):228-234.

D6: KAGAN G ET AL: "FLUFENAMIC-ACID AND PLACEBO COMPARED IN RHEUMATOID ARTHRITIS AND OSTEO ARTHRITIS" JOURNAL OF INTERNATIONAL MEDICAL RESEARCH, 1981, 9(4):253-256.

D7: BROELL H ET AL: "Long time therapy with Benzbromaron in patients with arthritis urica" WIENER MEDIZINISCHE WOCHENSCHRIFT, 1975, 125(38):546-548.

D8: HARRIS MARK ET AL: "Effect of low dose daily aspirin on serum urate levels and urinary excretion in patients receiving probenecid for gouty arthritis" JOURNAL OF RHEUMATOLOGY, December 2000 (2000-12), 27(12):2873-

2876.

D9: EP-A-1 136 552 (BAYER AG) 26 September 2001.

D10: HARRIS RICHARD R ET AL: "Clinical activity of leukotriene inhibitors" INTERNATIONAL JOURNAL OF IMMUNOPHARMACOLOGY, 1995, 17(2):147-156.

D11: LALIBERTE RON ET AL: "Tenidap modulates cytoplasmic pH and inhibits anion transport in vitro: II. Inhibition of IL-1-beta production from ATP-treated monocytes and macrophages" JOURNAL OF IMMUNOLOGY, 1994, 153(5):2168-2179.

D12: ROBERT J: "Multidrug resistance in oncology: Diagnostic and therapeutic approaches" EUROPEAN JOURNAL OF CLINICAL INVESTIGATION, June 1999, 29(6):536-545.

D13: ANDERSSON RONNY ET AL: "Effects of interferon-alpha, verapamil and dacarbazine in the treatment of advanced malignant melanoma." MELANOMA RESEARCH, February 2003, 13(1):87-91.

D14: YANG JIA-LIN ET AL: "Effect of nifedipine in metastatic colon cancer with DNA mismatch repair gene defect" LANCET (NORTH AMERICAN EDITION), June 2001, 357(9270:1767-1768.

D15: MIDTVEDT K ET AL: "Nifedipine slow release reduces the incidence of acute rejections in hypertensive renal transplant recipients" NEPHROLOGY DIALYSIS TRANSPLANTATION, September 1999, 14(9):A308.

D16: LAKE-BAKAAR G ET AL: "Dose-dependent effect of continuous subcutaneous verapamil infusion on experimental acute pancreatitis in mice" DIGESTIVE DISEASES AND SCIENCES, 1995,, 40(11):2349-2355.

D17: DONG RAYMOND ET AL: "Verapamil ameliorates the clinical and pathological course of murine myocarditis" JOURNAL OF CLINICAL INVESTIGATION, 1992, 90(5):2022-2030.

D18: APP E M ET AL: "ACUTE AND LONG-TERM AMILORIDE INHALATION IN CYSTIC FIBROSIS LUNG DISEASE A RATIONAL APPROACH TO CYSTIC FIBROSIS THERAPY" AMERICAN REVIEW OF RESPIRATORY DISEASE, 1990, 141(3):605-612.

D19: WOO T Y ET AL: "Nifedipine in scleroderma ulcerations." INTERNATIONAL JOURNAL OF DERMATOLOGY. DEC 1984,

23(10):678-680.

D20: ABE K: "Effect of nicardipine hydrochloride on ischemic brain edema" NEUROLOGIA MEDICO-CHIRURGICA, 1987, 27(9):819-824.

D21: BENEDETTI A ET AL: "Treatment with amiloride, a Na+/H+ exchanger inhibitor, reduces hepatic stellate cells activation and collagen deposition in experimental liver fibrosis" HEPATOLOGY, 1997, 26(4 PART 2):334A.

1.1 Unless indicated, reference is made to the passages indicated in the international search report.

2. Clarity (Art. 6 PCT)

2.1 Claim 1, its dependent claims 2-6 and 8-12, as well as claims 37-41 do not comply with the clarity, conciseness and/or support requirements of Article 6 PCT, because the functional definition of compounds given in claims 1 and 37, namely "one inhibitor of at least one ABC-transporter capable of transporting hyaluronan across a lipid bilayer", encompasses a genus of compounds defined only by their function wherein the relationship between the structural features of the members of the genus and said function have not been defined. In the absence of such a relationship, which has not been disclosed in the application as originally filed and which does not appear to be well recognized from information readily available to one skilled in the art, the skilled person would not know which group of compounds should be analysed for the uses of claims 1-6, 8-12 and 37-41. The fact that one could have assayed a compound of interest using the claimed assay or the assay specified in the description does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those specified in claim 7 or in claims 42-46) would fall within the scope of what is claimed. It would require undue experimentation, and hence undue burden to randomly screen undefined compounds for the claimed activity.

It is further noted that in general the definition of compounds in terms of functional parameters makes a complete search impossible. In this regard it is not always disclosed in the searched prior art documents whether the candidate compound(s) would fulfill the requirements of such functional parameters or not.

Consequently, the search has been carried out for those parts of the application which do appear to be clear and supported by the present description and for which a search is feasible, namely for the particular agents mentioned in present claims 7, 42-46.

2.2 Moreover, the term "disease associated with an excess transport of hyaluronan across a lipid bilayer" in present claims 1, 13, 15, 24, 28 and 37 is also considered to contravene Art. 6 PCT, since the person skilled in the art does not know which diseases are encompassed by such a definition. The applicant's attention is drawn to the fact that the discovery on which the invention is based (i.e. the inhibition of the hyaluronan transport across a lipid bilayer by an inhibitor of at least one ABC transporter), even if representing an important piece of scientific knowledge, still needs to find a new practical application in the form of the use of a compound for a defined disease in order to make a technical contribution to the art and be considered an invention eligible for patent protection.

Therefore, only those diseases mentioned on page 13, lines 4-24 have been taken into consideration for the search of the present patent application.

2.3 The fact that in the present set of claims an unclear definition for the compounds is combined with an unclear definition for the diseases for which said compounds are to be used makes the scope of protection of present claims particularly difficult to delimitate.

Consequently, the following opinion is drafted only for those parts that are clear, concise, supported and have therefore been searched, namely for those mentioned under items 2.1 and 2.2 above.

3. **Novelty (Art. 33(2) PCT)**

3.1 D1 discloses the use of inhibitors of the P-glycoprotein, which is the expression product of the MDR1 gene, for the treatment of rheumatoid arthritis. Inhibitors mentioned therein are cyclosporin, chloroquine and PSC-833, among others.

D2 also discloses that some well-known antiarthritic agents such as cyclosporin are inhibitors of the MDR system and mentions other MDR inhibitors as candidates for the therapy of arthritis.

3.2 D3 anticipates the use of Ca antagonists (verapamil, diltiazem, nifedipine, nicardipine, nimodipine and bepridil), calmodulin antagonists (chlorpromazine, trifuoperazine, fluphenazine, flupentixol and clopentixol), non-cytotoxic anthracyclines, cyclosporin and other agents (amiodarone, reserpin and chloroquine) for the treatment of arthritis. These agents are mentioned to inhibit the mdr1 glycoprotein.

Similarly, D4 relates to the use of Ca antagonists in the treatment of arthritis.

3.3 Further, D5 and D6 disclose the use of indomethacin and flufenamic acid in rheumatoid arthritis, respectively.

3.4 The studies in D7 and D8 show that benzbromaron and probenecid are used in the treatment of arthritis.

3.5 D12 concerns the use of MDR inhibitors in the treatment of different types of cancer.

3.6 D13 discloses that the combination of dacarbazine, IFNalpha2b and verapamil is more effective than dacarbazine alone in the treatment of advanced malignant melanoma.

3.7 D14 shows that nifedipine treatment causes remission of metastatic colon cancer.

3.8 D15 discloses that nifedipine reduces the incidence of acute rejection in hypertensive renal transplant recipients.

3.9 D16 shows that increasing doses of verapamil protect against diet-induced pancreatitis in mice.

3.10 D17 teaches that verapamil significantly reduces the microvascular changes and

myocardial necrosis, fibrosis and calcification leading to cardiomyopathy in encephalomyocarditis.

3.11 D18 discloses that amiloride is able to enhance mucus clearance favourably in patients with cystic fibrosis lung disease.

3.12 D19 shows that nifedipine therapy causes visible improvement of an ischemic ulcer of scleroderma.

3.13 D20 shows that nicardipine suppresses the development of late cerebral edema during recirculation following a 30-minute global ischemic insult in rats.

3.14 D21 discloses that amiloride has antifibrotic effect in the treatment of liver fibrosis.

3.15 Consequently, the subject-matter of present claims 1-12, 37-41 is not considered novel in the light of D1-D21.

4. **Inventive Step (Art. 33(3) PCT)**

4.1 The subject-matter of present claims 1-12, 37-41 is not novel and therefore cannot be considered inventive.

Nevertheless, the following should be also noted:

4.2 D9 discloses that glyburide inhibits IL-1beta secretion by inhibiting the ABC1 transporter and suggests its use for the treatment of inflammatory diseases such as rheumatoid arthritis.

D10 discloses that MK571 is a leukotriene inhibitor that could be useful for the treatment of rheumatoid arthritis.

D11 mentions that DIDS mimics the IL-1beta inhibitory action of the antiarthritic agent Tenidap.

4.3 Moreover, the subject-matter of claims 42-46 is not considered to involve an inventive step, the reasoning being as follows:

Said claims concern the use of concrete inhibitors of an ABC-transporter. Since it is known from D1 and D2 that inhibitors of the MDR system are useful in the treatment of arthritis, the person skilled in the art would expect that other substances having the same mechanism of action are also useful for the same purpose as that indicated in D1 or D2. Therefore, the subject-matter of claims 42-46 is considered obvious in the light of D1 or D2.

5. Industrial applicability (Art. 33(4) PCT)

5.1 Present claims 1-36, 42-46 are susceptible of industrial application and thus do not contravene Art. 33(4) PCT.

5.2 For the assessment of the present claims 37-41 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.